Zentralblatt für Bakteriologie, Parasitenkunde, Infektionskrankheiten und Hygiene · I. Abteilung

Supplement 8

Medical Mycology

Proceedings of Mycological Symposia of the XII International Congress of Microbiology

Munich, September 3–8, 1978

Edited by
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157 figures and 99 tables

Gustav Fischer Verlag Stuttgart · New York

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GUSTAV FISCHER VERLAG · STUTTGART · NEW YORK
1980

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CIP-Kurztitelaufnahme der Deutschen Bibliothek

Medical mycology : proceedings of Mycolog. Symposia of the XII. Internat. Congress of Microbiology, Munich, September 3 – 8, 1978 / ed. by Hans-Jürgen Preusser. – Stuttgart, New York : Fischer, 1980. (Zentralblatt für Bakteriologie, Parasitenkunde, Infektionskrankheiten und Hygiene : Abt. 1 : Suppl. ; 8) ISBN 3–437–10602–3

NE: Preusser, Hans-Jürgen [Hrsg.]; Mycological Symposia <1978, München>; International Congress of Microbiology <12, 1978, München>

Production: Graphischer Großbetrieb Friedrich Pustet, Regensburg
Printed in Germany

Preface

Due to the continously progressing propagation of mycoses all over the world, the scientific interest in research of ecology and biological phenomena of human pathogenic fungi has increased rapidly.

Studies on host-parasite interactions in fungal diseases, and the search for new methods in the fight against pathogenic fungi are focal points of recent mycological research. Additionally, the manifold chances of the infection with dermatophytes and the transmission of fungal germs from man to animal and *vice versa* are responsible for the worldwide spread of dermatomycoses. Medical mycology is, therefore, becoming of major importance to man and society. Evidence of this increasing interest was manifest at the XII International Congress of Microbiology in Munich/FRG, September 3–8, 1978, where, in 7 symposia more than 50 contributions on medical subjects were presented in the Mycology Section.

The recent increase of the serious impairment of the health of hospital patients, especially in gynecological wards, caused by infections with pathogenic yeasts signifies a worldwide problem; however, the dissemination of information about human infections caused by commensale fungi whose soil or plant born spores are spread by air has not been widespread enough. Multiple sources of infection by these opportunistic fungi are particularly evident in hospitals and other risk areas. Modern methods of therapy promote the distribution of mycoses in hospitals, e.g., the postoperative administration of antibiotics, and the therapy of neoplastic diseases with cytostatics. Often these mycoses are manifest by defects of the immune system of man. Effective antifungal agents will permit advances in the therapy of mycoses. Moreover, specific antibody tests could help clinicians in diagnosis of systemic mycoses. The development of new methods for isolation of antigens, studies of the antigenic structure and antigenic properties of agents causing systemic mycoses are further focal points in the research of medical mycology.

Diseases of man and animal caused by mycotoxins as contaminants of moulded foods and feeds increase in number worldwide. Intoxications appear not only directly after ingestion of infected plant material, but also indirectly by the uptake of mycotoxin residues in animals producing foods and fed with moulded nutriments. The development of new analytical methods for the detection of mycotoxins in body fluids and tissues are of increased interest for research as well as for public health.

In 46 topical contributions and comprehensive reviews this volume deals with advances in experimental investigations and gives an impression of the present state of research to mycologists, dermatologists, hygienists, and professionals in other fields of medicine interested in medical mycology.

I would like to express my thanks to both contributors and conveners of the symposia whose assistance made possible the successful aims of this project. I am especially indebted to Mrs. Heidi Rostek for her excellent cooperation, for revising the proofs and elaborating the subject index, and to Mrs. Regina Lahtz, Gustav Fischer Verlag, Stuttgart, for carrying out the correspondence with contributors and conveners.

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Chapter 1

Dimorphism

Preusser (eds.): Medical Mycology, Zbl. Bakt. Suppl. 8
Gustav Fischer Verlag · Stuttgart · New York · 1980

Dimorphism and Antigens

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Introduction

A number of fungi which produce visceral mycoses are able to exist in two forms, mycelial and yeast, differing from one another in morphology, physiological and biochemical activity, antigenic properties, resistance to inhibitory and other features. The mycelial form is characteristic of fungi during their habitation in the environment and under the usual conditions of cultivation in the laboratory; the yeast form of dimorphic fungi occurs in the tissues of a human or animal host and *in vitro* under special conditions of cultivation. Conversion of cells from one form to another is induced by certain external factors and takes place when the fungus is incubated under appropriate conditions. The process of conversion from one form to another is a useful model for the study of fungal gene expression. Infections caused by dimorphic fungi are of particular interest for investigation of anti-infection immunity and microbe-host interactions in the dynamics of chronic infection.

The unique feature of the immune reaction in cases of mycoses caused by dimorphic fungi is the fact that the immune response is formed against a pathogen whose biochemical and immunological properties change during the process of conversion from the saprophytic into the parasitic form of growth.

That is precisely why, when working out methods of immunodiagnosis, immunoprophylaxis, and immunotherapy of such mycoses, a comparative immunochemical characterization of the mycelial and yeast forms of the pathogens and an evaluation of immunobiological activity of products of fungus activity during different stages of its development becomes absolutely necessary. In this paper these questions will be considered on the basis of the publications of others and of results obtained by coworkers from our laboratory.

M→Y conversion of dimorphic fungi

Conversion of dimorphic fungi from the mycelial to the yeast form (M→Y conversion) is caused by different physical, chemical, and biological factors. Of the physical agents bringing about M→Y conversion in fungi temperature has been the most extensively studied. Thus, a temperature increase from 28° C to 37–41° C brings about a conversion of mycelial cells into yeast (or spherule) cells in *Blastomyces dermatitidis* (29, 34), *Paracoccidioides brasiliensis* (34), *Histoplasma capsulatum* (2, 49), and *Emmonsia crescens* (13, 53, 54). In many dimorphic fungi, e.g., *H. capsulatum, Coccidioides immitis, E. crescens* and *Sporothrix schenckii* temperature conversion of the mycelial form to the yeast (or spherule) form involves both the effect of temperature and some additional culture conditions. Thus, in *S. schenckii, H. farciminosum* and *Cladosporium werneckii* M→Y conversion increases when the fungus is grown in an increased CO_2 content in the air (2, 12, 18). The conversion of mycelial to yeast cells observed when fungi are cultivated in liquid media

or that observed after inoculation of the medium with a large inoculum is reported to be due to the increased CO_2 content under these conditions (43).

When *H. capsulatum* is grown in animal histiocytes of different species it has been shown that a drop in temperature from 37° C to 25 °C was accompanied by a germination of some yeast cells, though in some histiocytes the fungus still remained as a blastospore even at the temperature of 25° C (19). In *E. crescens* the formation of spherules after a temperature increase *in vitro* is possible only upon protein and thiamine enriched media at pH higher than 6.0 (50, 53).

For M→Y conversion of *H. capsulatum* and *C. werneckii* it is necessary to add a sulfhydryl compound into the culture medium (18, 35–37, 49), and for *H. capsulatum* one must besides add B vitamin (35–37, 49) and chelates binding the ions of Ca^{++} and Mg^{++} (40). In the opinion of MARESCA et al., cysteine added to the culture medium affects the process of M→Y fungus conversion through the system of cell cyclic AMP-phosphodiesterase (31).

Spherule formation of *C. immitis in vitro* is promoted by cultivation in liquid shake cultures (4), and also by the addition of surface-active substances into the medium (5, 6), of sulfhydryl components (6), and of metal ions and other metabolites (15). In the majority of cases the components of the culture medium contributing to M→Y conversion provide also for fungus growth in the corresponding phase. However, prolonged cultivation of *H. capsulatum* in the yeast phase could be accomplished at a temperature of 25° C, if the medium was provided with a sufficiently high content of SH groups (37, 49). At the same time fungus conversion from the mycelial to the yeast phase at a temperature lower than 37° C failed. For effective germination of *H. capsulatum* blastospores it was necessary to grow the fungus not only at 25° C, but also upon a rich culture medium with a certain relative content of amino acids and vitamins in it (55).

Biochemistry of dimorphic fungi

Fungi in the mycelial and yeast or spherule phases differ in their requirement of vitamins and supply of nitrogen and carbon.

In comparison with mycelial, yeast cells of many fungi are characterized by a more active respiration, a capacity to oxidize exogenous acetate and glucose (34). Yeast and mycelial cells of *B. dermatitidis* differ as to spectrum and activity of malate dehydrogenase, the key enzyme in the metabolism of carboxylic acids in the cell (45).

In order to explain the effect of CO_2 upon M→Y fungus conversion it was assumed that CO_2 in anaerobic conditions can activate fungi carboxylases with CO_2 inclusion in the carbohydrates of yeast phase cell walls (1).

In *H. capsulatum* the rate of uptake and incorporation of some amino acids and purines into proteins and nucleic acids by mycelial cells is higher than in blastospores (51).

As is known, in microorganisms the form of the cell is determined by the cell wall. Therefore, particularly careful attention has been paid to the chemical structure and antigenic properties of cell walls of dimorphic fungi. The chief components of cell walls of dimorphic fungi (mycelial and yeast phase) are lipids, glucans and proteins.

The lipid content in the cell walls of the mycelial and yeast phases of certain fungi e.g., *P. brasiliensis* and *H. capsulatum* may be the same (22, 34) while in others, i.e. *B. dermatitidis* the mycelial cells are more than 2 times richer in lipids (8).

In the majority of dimorphic fungi, yeast phase cell walls turn out to be richer in chitin and poorer in amino acids, proteins and mannose (9, 11, 22). Glucans in the cell walls of mycelial and yeast phases differ somewhat in their physico-chemical properties (22). Thus, the cell wall of the mycelial phase of *H. capsulatum* had glucans with β-glucoside bonds, and in the walls of the yeasts there were glucans with both α-glucoside (60%) and β-glucoside (40%) links (21).

At the same time, cell wall glucans of different fungus strains of the same species and the same phase may also differ in their structure, and consequently in their sensitivity to α- or β-glucanases (7, 42).

In some dimorphic fungi the virulence of different strains correlates with the peculiarities of their

cell wall structure. Thus, in P. brasiliensis the decrease of pathogenicity after prolonged fungus cultivation *in vitro* was accompanied by a decrease of α-1.3 glucan, and an increase of galactomannan in the cell walls (48). The more virulent mutant of *P. brasiliensis*, on the contrary differs from the parental strain in a high α-1.3 glucan content in the cell wall, and practically a complete disappearance of galactomannan (47).

H. capsulatum yeast and mycelial phase cell walls pretreated with trypsin and pepsin differ somewhat in amino acid composition. In *H. capsulatum* yeast cells the characteristic properties of the wall amino acid composition is correlated with the serotype of the fungus; the amino acid composition of the cell walls of different serotypes of mycelial phase *H. capsulatum* are quite similar (38).

The structural peculiarities of the cell wall of dimorphic fungi, determine not only the antigenic specificity but also correlates with differences in the sensitivity of yeast and mycelial cells to antibiotics. Thus, *H. capsulatum* in the mycelial phase is more sensitive to amphotericin-B and clotrimazol than is the yeast phase. On the contrary, the yeast phase is more sensitive to actinomycin and a combination of cycloheximide and chloramphenicol than is the mycelial phase (3). Addition of certain antibiotics to the culture medium, even in the presence of other optimal conditions, inhibits fungi conversion from one phase to another (3).

It is possible to derive antigenic preparations differing in chemical composition with different solvents from cells of various phases of dimorphic fungi. Thus, in our experiments preparations obtained by extraction of *B. dermatitidis* and *H. capsulatum* mycelial cells with β-napthol differed from extracts of yeast phase cells in having a higher relative carbohydrate content (1.9–2.0 times), and a lower content of proteins (3.8–4.5 times) and nucleic acids (8.5–17.0 times) (23). With respect to carbohydrates fungi in their mycelial and yeast phases differed in the relative content of some monosaccharides. Glucose, mannose, galactose, hexosamine and trace amounts of some other monosaccharides were identified in the carbohydrate composition of both mycelial and yeast cells. Carbohydrates of the mycelial phase were richer in glucose, and of the yeast phase in mannose; hexosamine content was somewhat higher in yeast cells. Yeast phase *H. capsulatum* and *B. dermatitidis* polysaccharides contain chiefly mannanogalactans, and the mycelial phase chiefly glucomannans (23).

Dimorphic fungi in different phases of development may differ not only in their chemical structure and metabolism, but also in their capacity to excrete various biologically active metabolites into the medium. In joint experiments with A. G. YARMUKHAMEDOVA we compared certain isoenzymes, proteins and antigens which are present in dimorphic fungi intracellularly, and which are excreted into the culture medium during different phases of fungus development. We used *E. crescens* in which the mycelium converts (saprophytic phase) to adiaspores (parasitic phase) both in vivo and in vitro.

In order to obtain mycelial biomasses and culture spherules *E. crescens* was grown on a glucose-asparagine medium at 28° C and 37° C, respectively for 2 and 4 weeks. The treatment stages of the culture filtrate from the saprophytic and parasitic phases of the fungus, and the isolation, disruption and the subsequent fractionation of mycelial cells and of adiaspores of *E. crescens* are presented diagramatically in Fig. 1. The content of mature spherules (adiaspores) in the preparation that was used for ultrasonic disintegration was 80–85% (both adiaspores and mycelium fragments were counted). For a comparative immunochemical investigation we used adiaspore and mycelium cell sap (the supernatant after ultrasonic disintegration and centrifugation for 90 min at 105000 g), and culture filtrates from the mycelial and sperule phase. The protein content of the preparations was determined (30), and enzymoelectrophoretic analysis was carried out on polyacrylamide gel (15% polyacrylamide gel 3 mm thick, pH-8.3; 0.025 mg of protein per 1 mm^2 of gel cross section, division during 4 hours at a voltage of 2 V/mm^2 and a current of 0.1 mA) (33). After electrophoresis the plates were cut into parallel bands, in which, with the help of chromogenic substrates, we tested for lactate dehydrogenase (E.C. 1.1.1.27), malate dehydrogenase (E.C. 1.1.1.37), succinate dehydrogenase (E.C. 1.3.99.1), catalase (E.C. 1.11.1.6), peroxidase (E.C. 1.11.1.7), alkaline (E.C. 3.1.3.1) and acid (E.C. 3.1.3.2) phosphatase, esterase of ethers of carboxylic acids, and by the contact method the activity of amylase and lipase (E.C. 3.1.1.3) (33).